REMARKS/ARGUMENTS

STATUS OF THE CLAIMS.

Claims 1, 4-9, 12, and 14-15 are currently pending in the application with entry of this amendment. Claims 1, 4 and 12 are amended herein to more clearly describe embodiments of the invention, claims 2, 3, and 13 are cancelled, and claims 16 and 17 are newly added. These changes introduce no new matter and support is present in the application and claims as originally filed. The changes are made without prejudice and are not to be construed as abandonment of any previously claimed subject matter or agreement with any objection or rejection of record. Accordingly, entry of the Amendment is respectfully requested.

NEW CLAIMS.

Claims 16 and 17 are newly added herein. Support for such new claims can be found, *e.g.*, at the first paragraph of page 5, the first full paragraph of page 6, and the second full paragraph of page 23. Therefore, these changes introduce no new matter and their entry is respectfully requested.

REJECTIONS TO THE CLAIMS

35 U.S.C. §112 Second Paragraph.

Indefiniteness

Claims 1-9 and 12-15 were rejected in the current Office Action under 35 U.S.C. §112, second paragraph, as allegedly indefinite by failing to particularly point out and distinctly claim the subject matter regarded by applicants as the invention. To the extent that the rejections are applied to the amended claims, Applicants traverse.

The claims were rejected as allegedly unclear in their use of the words "modulates" and "modulating." The Office Action argues that such terms are indefinite and that no definition is "provided that sets forth what properties distinguishes a modulator from and [*sic*] activator or inhibitor." Applicants respectfully traverse.

As is clear from page 11 (final paragraph) and its usage throughout the application as filed, the term "modulate" and its various derivatives are used as descriptors to encompass compounds that are inhibitors, activators, agonists, antagonists, etc. For example, line 10, page 26 illustrates that modulators (*i.e.*, compounds that modulate or that are modulating) as a group include agonists and antagonists. A common definition of "modulate" includes "change." *See, e.g.*, the definition of "modulate" at www.thesaurus.com. Thus, in the present application, molecules that are "modulators" of TC-ICS should be taken to include those that change or alter taste transduction directly or indirectly whether such change is inhibitory, stimulatory, partially inhibitory to various degrees, partially stimulatory to various degrees, etc. Because the terms "modulates" and "modulating" are clear from the application as filed Applicants respectfully request that the rejection be withdrawn.

The claims were also rejected as allegedly indefinite for use of the phrase "functional effect." Applicants respectfully traverse.

The Office Action states that the phrase "functional effect" is indefinite because the definition of it on page 11, uses the phrase "under the influence of TC-ICS" which is allegedly undefined while the rest of the definition of "functional effect" is solely by way of examples.

The determination of indefiniteness is whether "those skilled in the art would understand the scope of the claim when the claim is read in the light of the specification." *Breuer Electric Mfg. Co. v. Tennant Co.*, 44 USPQ2d 1259, 1266 (Ill. 1997). Applicants submit that those of skill in the art would grasp the scope of a "functional effect" of a compound on parameters "under the influence of TC-ICS." The specification gives a large number of examples of such effects on parameters that can be under the influence of TC-ICS, *e.g.*, changes in ion flux, changes in membrane potential, etc. (page 10) and how to measure/quantify them, *e.g.*, via patch clamp, etc. (page 11). Additionally, starting on page 23 the section entitled "Assays for taste cell-specific ion channel subunit activity" describes numerous functional effects on parameters that can be controlled/influenced by TC-ICS and how to measure or quantify them. Furthermore, claim 1 is amended herein to incorporate the limitations of prior claims 2 and 3. Thus, amended claim 1 comprises determining functional effects including: changes in intracellular ion concentration, changes in a transmembrane ion flux; and, changes in intracellular Ca^{++}. Descriptions of such functional effects and methods of measuring such functional effects, and cites to references

illustrating such effects and ways of measurements are shown, *e.g.*, at page 25 (discussing intracellular Ca^{++} levels, changes in ion flux, etc.).

Thus, because of the numerous examples given in the specification and the high level of skill in the art, those of skill in the art are easily able to understand what is claimed when the claim is read in light of the specification. Therefore, the claims are not indefinite and Applicants respectfully request that the rejection be withdrawn.

The claims were also rejected as allegedly indefinite in the use of the phrase "forming a functional ion channel" as used in claim 1. Applicants respectfully traverse.

The Office Action alleges that the specification does not set forth the procedure for determining whether the polypeptide of SEQ ID NO: 8 is functional or not. However, the proper standard is whether those skilled in the art would understand the scope of the claim when it is read in light of the specification, *i.e.*, whether those of skill in the art understand what is meant by "forming a functional ion channel."

As described above, the level of skill in the area is high (*e.g.*, as shown by the numerous citations listed, the fact that ion channel molecules as a class are known, etc.). The phrase means precisely what it says. One of skill knows what each word of the phrase means, and as evidenced by the teachings already noted, can easily determine whether a functioning ion channel is formed. That is, as set forth above, there are numerous assays which are well known to those of skill in the art to measure whether ion channels are functional.

Therefore, because of the plain language at issue and the numerous examples given, *e.g.*, of how to quantify effects of modulators on parameters under the influence of the TC-ICS ion channel and, thus, how to quantify functionality of the ion channel, and the high level of skill in the art, those of skill in the art fully comprehend the limitation. Therefore, Applicants respectfully request that the rejection be withdrawn.

Finally, the claims were rejected as allegedly indefinite based on their use of the word "predetermined" in claim 1(ii). While Applicants believe the term to not be indefinite as used, in order to further prosecution and to more clearly claim the current embodiment, Applicants herein amend. Applicants herein amend claim 1(ii) to remove the "a transmembrane ion flux of a

predetermined ion" and replace it with "the cell or cell membrane which expresses the taste cell-specific ion channel subunit," etc. Direct support for such word change can be found, *e.g.*, in the third and fourth paragraphs of page four, the first full paragraph on page 6, etc. Because the wording upon which the rejection was based is removed, Applicants respectfully request that the rejection be withdrawn.

35 U.S.C. §112 First Paragraph.

Enablement

Claims 1-9 and 12-15 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. To the extent that the rejections remain after the current amendments, Applicants respectfully traverse.

As put forth in M.P.E.P. §2164.01, the test for enablement is whether those reasonably skilled in the art can make or use the invention based on the disclosures in the patent, along with information known in the art, without undue experimentation. In fact, it is preferable to omit that which is well known in the art. *See, e.g.*, M.P.E.P. §2164.01; *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, (Fed. Cir. 1998); and, *In re Buchner*, 929 F.2d 660, 18 USPQ2d 1331, (Fed. Cir. 1991). Just because experimentation may be complex does NOT necessarily make it undue if the art typically engages in such experimentation. The test for undue experimentation is not just quantitative "since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

A number of nonlimiting factors are put forth in M.P.E.P. §2164.01(a) to aid in determination of whether experimentation is undue, *e.g.*, the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The Office Action contends that in order to practice the invention, one skilled in the art would need to know which assays and which materials could be used in conjunction with the

polypeptide of SEQ ID NO: 8. The Office Action also contends that the specification "admits that it is well recognized in the art that the signal transduction schemes underlying taste transduction are bewilderingly complex and poorly understood," and that it would require an extensive (and unduly burdensome) research plan to try to use the invention as claimed. Applicants respectfully traverse.

Applicants point out that the specification does not state that the transduction schemes underlying taste transduction are "bewilderingly complex and poorly understood" as asserted by the Office Action. In the Background on page 3, in the context of the prior art, the specification states that "very little is known about the molecules and pathways that mediate these sensory signaling responses"; that most of the "molecular components of the sour or salty pathways have not been identified"; and that "there are almost as many models of signaling pathways for sweet and bitter transduction as there are effector enzymes for GPCR cascades."

However, the specification does not state that little is known about the different effects that various modulators can have on the cell/cell membrane (*e.g.*, changes in certain ion concentrations, changes in membrane potential, etc.) nor does the specification state that little is known about how to measure or quantify such effects (*e.g.*, via patch clamps, etc.). In fact, much is known about ion channels in general and about what to measure and how to measure it in order to determine activity of ion channels, etc. For example, pages 8, 10-11, and 23-28 all discuss examples of assays on various effects influenced by ion channels, *e.g.*, the sequences of the invention. Thus, page 25 discusses and gives examples of changes in intracellular Ca^{++} levels (and ways to measure such), changes in ion flux (and ways to measure such), etc., as well as citations to references presenting further detail and guidance.

Also, applicants point out that, as emphasized throughout the specification as filed and as evidenced by the numerous citations given within the specification, those of skill in the art are extremely familiar with, and routinely perform, assays and experimentation to measure/quantify functional effects of modulators on cells/cell membranes, *e.g.*, by measuring ion flux, changes in intracellular Ca^{++}, etc. Furthermore, the level of skill in the area is quite high, and the specification cites to multiple journal articles detailing protocols to guide those of skill in the art in any experimentation. Because the level of skill in the art is high, the specification cites to numerous sources of guidance, and the types of experiments that might be needed are those that are routinely

performed in the art, the breadth of the claims is fully enabled and Applicants respectfully request that the rejection be withdrawn.

The Office Action further rejects the claims based on the limitation in claim 1(ii) of "determining a functional effect of the compound upon a transmembrane ion flux of a predetermined ion." Because the claim language upon which this rejection is based has been amended, the rejection is moot and Applicants respectfully request that the rejection be withdrawn.

The Office Action also rejects the claims as allegedly lacking enablement based on the requirement of claim 1(i)(b) of forming a functional ion channel. Applicants respectfully traverse. Again, the level of skill in the art is quite high. As explained above, the specification gives examples of types of assays used to determine functional effects influenced by ion channels, and hence, to determine activity of the ion channel. The specification also cites to many references which give protocols and examples of ways to determine if an ion channel is functional, etc. Therefore, to those of skill in the art it would not be unduly burdensome to determine if a functional ion channel had been formed, and Applicants respectfully request that the rejection be withdrawn.

The Office Action rejects claims 12-15 as allegedly lacking enablement because there is no teaching of compounds that directly modulate the activity of the polypeptide of SEQ ID NO: 8. Applicants point out that such rejection is moot since Applicants herein amend claim 12 to recite requirements in identifying compounds, thus, allowing the selection of the compounds. Therefore, because the language upon which the rejection was based has been modified, Applicants respectfully request that the rejection be withdrawn.

The Office Action also rejects the claims as allegedly lacking enablement for amino acids other than the sequence present in SEQ ID NO: 8. Applicants respectfully traverse.

The Office Action alleges that the specification "provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change, *e.g.*, such as by amino acid substitutions or deletions," and that the application "does not provide any

information as to where these sites of conservative variation, non-critical residues, or non-critical regions could be – such information being necessary to enable the skilled artisan to make and use the claimed invention without undue experimentation."

However, Applicants respectfully point out that the specification does indeed provide such guidance. The application provides three TC-ICS sequences (rat, mouse, and human), instructions on how to find homologous ion channel sequences in databases, and citations to multiple other TRP family ion channels. All such sequences can be aligned to determine both areas that are conserved between species, etc., and those regions that are not highly conserved between species, etc. As pointed out in the prior Response, the level of skill in making conservative amino acid substitutions, *e.g.*, in choosing substituents to be incorporated in non-highly conserved areas without loss of functionality in a sequence, is quite high. Thus, one of skill in the art could align and compare the given sequences along with the sequences of other known TRP family ion channels in order to determine areas for substitution, etc. Because the specification provides sequences and instructions for finding other sequences as well as comparing sequences to determine conserved regions, etc., those of skill in the art would not face undue experimentation in determining areas wherein sequence variation can be introduced, as well as the types of sequence variation, *e.g.*, conservative substitutions, especially since such determinations are routine in the art.

As explained above, determining which of such sequences produces a functional ion channel, is not unduly burdensome, given, *e.g.*, the level of skill in the field and the amount of guidance presented within the specification as filed. *See above.* Therefore, Applicants respectfully request that the rejection be withdrawn.

Written Description

Claims 1-9 and 12-15 were rejected in the Office Action as allegedly lacking adequate written description under U.S.C. §112, first paragraph. To the extent that the rejections are applied to the amended claims, Applicants respectfully traverse.

In order to satisfy the written description requirement, M.P.E.P. §2163(I) states that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention."

The Office Action alleges that in order to practice the invention, one skilled in the art would need to know which of the assays presented in the specification could be used in conjunction with SEQ ID NO: 8. The Office Action also alleges that given the teachings in the specification and the general knowledge in the art that only the patch pipette technique could be used. Applicants respectfully traverse.

The claims as amended are drawn to determination of a functional effect of the compounds as measured by a change in intracellular ion concentration, a change in a transmembrane ion flux of an ion, or a change in intracellular Ca^{++}. Methods of determining these effects are described in the specification (*see, e.g.*, pages 23-28, etc.) with numerous citations for additional guidance for those of skill in the art. Given the extensive teachings provided, it is clear that the inventors were in possession of the claimed invention.

The Office Action also alleges that the formation of a functional ion channel is not adequately described in the specification. Applications respectfully traverse.

Again, the specification describes numerous tests and assays (*see, e.g.*, pages 23-28) to use in determination of functionality of ion channels (*e.g.*, patch clamps, etc. to measure ion flux, etc.). Additionally, the specification describes ways of defining controls to aid in determination of functionality of an ion channel. *See, e.g.*, pages 12 and 26. Given this teaching, the specification clearly shows that the inventors were in possession of the invention. Therefore, Applicants respectfully request that the rejection be withdrawn.

The Office Action alleges that claims 12-15 lack adequate written description because they do not teach compounds that modulate activity of the polypeptide of SEQ ID NO: 8. Applicants respectfully point out that an aspect of claims 12-15 is the identification of such compounds. The claims are herein amended to clarify such requirement. Thus, the rejection is moot in light of the amendments to the claims and Applicants respectfully request that the rejection be withdrawn.

The Office Action alleges that the claims are lacking in adequate written description in view of variants within 90% identity of SEQ ID NO: 8 yet which retain the required functional limitations. Applicants respectfully traverse.

The Office Action contends that disclosure of only three polynucleotides is not enough to adequately support the claimed genus of polypeptides since only one of the sequences (SEQ ID NO: 8) is more than 90% identical to itself.

However, in *Eli Lilly* (119 F.3d 1568, 43 USPQ2d 1398, 1406), it was held that a

> description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Similar to *Lilly*, the present application has a representative number of sequences, *e.g.*, the sequences listed in the application (even if not all within 90% identity with one another) as well as other ion channel subunits known to those of skill in the art which can be used in alignment to discern areas of conserved functionality. Additionally, such areas of conserved functionality give relevant identifying characteristics such as common structural features which can be coupled with functional characteristics (*e.g.*, as measured by the assays described in the specification) sufficient to show possession of the claimed genus. Furthermore, such alignments and determinations of conserved structure coupled with functionality are routine to those of skill in the art.

Therefore, the sequences disclosed, *e.g.*, when aligned with other ion channel sequences would allow those of skill in the art to discern common structural features and functions sufficient to describe a representative number of species in the genus and, thus, show that Applicants were in possession of the invention. Therefore applicants respectfully request that the rejection be withdrawn.

The Office Action alleges that the specification is lacking adequate written description in terms of verifying functionality of an ion channel. Applicants respectfully traverse.

The Office Action alleges that the numerous teachings on pages 23-28 simply serve as a "survey of general methods of studying signal transduction and not as specific instructions to be used to verify the functionality of a polypeptide of SEQ ID NO: 8." The Office Action also alleges that since no ligand is taught, then one cannot know if the ion channel is functional.

However, those of skill in the art would not view the many examples on pages 23-28 as general methods not to be applied to determining the functionality of the polypeptides of the invention. The heading of the section is "Assays for taste cell-specific ion channel subunit activity." The opening paragraph of the section directly states that the activity of TC-ICS polypeptides can be assessed via a number of methods and that such assays can be used to screen for activators, inhibitors, and modulators of TC-ICS. Since the invention is based on a TC-ICS and the specification segues directly into description of methods/assays to determine functionality of TC-ICS, it is clear that the assays presented were for use in relation to the current invention and not just a general survey of signal transduction. Furthermore, the specification describes controls, *e.g.*, page 12 and 26 which would aid those skilled in the art to determine functionality.

Because the assays are intended to be used in relation to the current invention and the specification explains ways to determine functionality of an ion channel, the invention is thus described so that those of skill in the art would realize the inventors had possession of the invention. Applicants therefore respectfully request that the rejection be withdrawn.

U.S.C. §102(e)

Claims 1-6, 8, 12, and 15 were rejected under 102(e) as allegedly anticipated by US patent Publication 2002/0037515 published March 28, 2002 which claims priority to USSN 60/197,491 filed April 17, 2000. Applicants respectfully traverse.

In the prior Response, Applicants filed a Declaration under 37 C.F.R. §1.131 putting forth the timeline of invention and showing completion of the invention prior to April 17, 2000. The current Office Action characterizes Applicants' prior Declaration as "simply assert[ing] possession of a clone (clone 501) before April 17, 2000" and not establishing completion of the invention prior to April 17, 2000. However, Applicants respectfully point out that the Declaration actually presents much more than just possession of clone 501 before April 17, 2000.

As presented in the Declaration, and as detailed in the prior Response filed April 28, 2005, not only was clone 501 in the possession of the Applicants prior to April 17, 2000, but such clone had already been used as the basis of BLAST searches. Such searches identified the Trpm5 mouse ortholog of the rat gene (which comprises the sequence of clone 501). The mouse ortholog and the human Mtr1 gene were found to have a high level of homology, thus, leading the Applicants

to recognize human Mtr1 as the ortholog of mouse Trpm5. Additionally, not only had the human and mouse orthologs of the gene been identified, but *in situ* hybridization experiments had been done to confirm the taste cell-specific expression of the rat version of the gene.

Thus, the human Mtr1 gene (which sequence was available prior to April 17, 2000) as well as the mouse Trpm5 gene (which sequence was available prior to April 17, 2000) and the rat sequence (from which clone 501 was derived by the inventors) were all identified by the inventors as genes for taste cell specific ion channels prior to April 17, 2000. Once identified as taste cell-specific ion channels, the ability to screen for modulators of the channels is plain.

Thus, because the present invention was completed prior to the earliest priority date claimed by US Patent Publication 2002/0037515, such publication cannot serve as a prior art reference under 35 U.S.C. § 102(e) and Applicants respectfully request that the rejection be withdrawn.

U.S.C. §102(b)

Claims 12-15 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Madden *et al.*, *Hepatology* 26(1):40-48, 1997. Applicants herein amend claim 12, cancel claim 13, and traverse to the extent that the rejections are applied to the amended claims.

The Office Action alleges that claims 12-15 not only are anticipated by Madden, but that they also read on the act of eating. In order to further prosecution and to more clearly claim the current embodiment, Applicants herein amend claim 12 to require that the method of modulating taste signaling in an individual includes identifying a compound that modulates taste signaling by determining a functional effect of the compound on the cell, etc., and administering such compound to the individual. Support for such changes is replete throughout the application as filed. For example, the first paragraph on page 4, read in light of the third paragraph on page 4, as well as the final paragraph of page 49, give support for the current changes. The limitations of claim 13 are incorporated into amended claim 12, thus claim 13 is cancelled herein. Because the changes present no new matter, their entry is respectfully requested.

In order for a reference to anticipate a claim "the reference must teach every element of the claim." M.P.E.P. §2131. Additionally, "every element of the claimed invention must be identically shown in a single reference," and the "elements must be arranged as in the claim under

review." *See, In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). Applicants respectfully submit that Madden does not teach every element of the amended claims. For example, Madden does not teach methods of modulating taste signaling in an individual comprising identifying compounds that modulate taste signaling by determining a functional effect of the compound on a cell comprising a taste cell-specific ion channel subunit, etc., and administering such compound to the individual as recited in amended claim 12.

Because Madden does not recite all of the limitations of the claims as amended, Applicants respectfully request that the rejection be withdrawn.

U.S.C. §102(anticipated)

Claims 1-4 were rejected under U.S.C. §102(anticipated) as allegedly anticipated by the abstract of Bernhardt, *et al.*, *J. Physiol.*, 490:325-336, 1996. Claims 1, 2, and 4-7 were rejected under U.S.C. §102(anticipated) as allegedly anticipated by Doolin, *et al.*, *J. Gen. Physiol.*, 107:545-554, 1996. Both references allegedly anticipate the current claims in regard to SEQ ID NO:2. While it is not stated, Applicants assume the rejections to be U.S.C. §102(b). As pointed out by the Examiner on page 2 of the current Office Action, the claims are currently only under examination to the extent that they read on elected SEQ ID NO:8. However, Applicants preliminarily address such anticipated rejections herein. Applicants respectfully traverse.

Applicants note that neither Bernhardt nor Doolin present all of the elements of the current claims. For example, neither of the cited references present the element of "determining a functional effect of the compound upon the cell or cell membrane which expresses the taste cell-specific ion channel subunit, wherein the functional effect is under the influence of the taste cell-specific ion channel subunit," as is required in the current claims. Neither of the references even examines the role that the ion channel has on the functional effect being measured. Thus, because neither of the references presents all of the elements of the current claims, neither of them can anticipate the current claims. Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. In the event that substantive matters are felt to remain, the Examiner is invited to telephone the undersigned at (510) 769-3507.

QUINE INTELLECTUAL PROPERTY LAW
GROUP, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,

Paul B. Littlepage
Reg. No: 48,581